Remarks

Claims 1-4, 7-11, 30, 31, 34-36, 42, 43, 49, 55 and 59-73 are pending in the application. Claims 61-63, 66-68 and 70-71 have been cancelled without prejudice and without admitting anticipation or obviousness. The relevant subject matter of Claims 61-63, 66-68 and 70-71 have been incorporated into amended claims 60, 65, and 69, respectively.

Although Examiner originally required a restriction of Claims 56-68 (Group V), Claims 59, 62-64 and 68 (Group VI) and Claims 60-61, 65-67, 69-73 and 68 (Group VII), it appears that the Examiner has rejoined these claims to the current application since no formal withdrawal of the claims is indicated on the office action summary and the claims have been included in the rejections. Consequently, applicants are assuming that these claims form a part of the current application.

In an attempt to expedite the current application to allowance, Applicants have limited the method claims to the treatment of Obesity. The amendment of the claims to Obesity should not be considered as an admission of unpatentability of the deleted subject matter and Applicants reserve the right to pursue the methods of use for other indications in one or more continuation applications.

§103 Rejections

I. Claims 1, 4, 30 and 55 were rejected under 35 USC §103(a) as being unpatentable over Aebi, et al., (CA 62:29669).

Examiner asserts that compound RN 848-61-3 is merely a homolog of the compounds of the present invention where R^1 is ethyl. However, Examiner has failed to recognize two very important teachings (or lack thereof) by Aebi.

First, Aebi does not disclose, teach, or even suggest compounds of Formula (II). The few compounds disclosed by Aebi are all directed to 4-keto pyrrolo-[3,4-c]pyrazoles (e.g., derivative compounds of Formula (I)).

Second, unlike the present invention, the only derivatives of 4-keto-pyrrolo-[3,4-c]pyrazoles disclosed by Aebi are those where R_4 (Applicants' R^1 position) is methyl. See, Table 4, page 621 of Aebi. This would imply that a methyl group is critical for this position and cannot be varied since all of the other positions (R_1, R_2, R_3 and R_5) were varied. In addition, Aebi states the following on page 618 (just below the structure XI).

"In animal experiments, **some** of the 4-keto-pyrrolo-[3,4-c]pyrazoles obtained manifest a moderately strong **anti-inflammatory** efficacy." (emphasis added)

Clearly, Aebi provides no teachings, suggestions or motivation to modify the compounds of Aebi in designing compounds that could be used as CB-1 antagonists for treatment of diseases mediated by the CB-1 receptor. Only some of Aebi's compounds showed efficacy and that efficacy was for anti-inflammatory effects without any disclosed or proposed mechanism of action. Unlike the present invention, the compounds disclosed by Aebi are exclusively compounds where R^1 is methyl. Only six of the thirteen compounds disclosed have an unsubstituted phenyl group attached at the R^0 position and of those only one has an unsubstituted phenyl group attached at the R^4 position (Aebi compound RN 848-61-3). Aebi states that only "some" of the compounds disclosed provided *in vivo* efficacy and Aebi did not disclose which of the disclosed compounds possessed such efficacy. Consequently, Aebi provides no teachings or motivation to produce the compounds of the present invention which act as CB-1 antagonists (or inverse agonists).

Examiner goes on to assert that one of skill in the art would be motivated to modify Aebi's compound RN 887-67-2. Not only does RN 887-67-2 differ from the presently claimed compounds by a methyl group attached at the R^1 position but also a hydrogen at the R^4 position. Clearly, as pointed out above, Aebi provides no motivation to modify the R^1 position (Aebi's R_4 position) since all of Aebi's compounds have a methyl group at this position. In addition, Aebi fails to provide any teachings or suggestions for any modifications to provide efficacious compounds, in particular compounds that would bind to and mediate the CB-1 receptor.

Applicants respectfully submit that Examiner has failed to establish a *prima facie* case of obviousness; therefore, the rejection must be withdrawn.

The same would be true of the Dohrn reference cited by Aebi. Applicants would like to point out that, unlike the present invention, Dohrn teaches compounds where R^{3a} or R^{3b} is a phenyl or substituted phenyl.

§112 Rejections

I. Claims 1-4, 7-11, 30, 31, 34-46, 42, 43, 49, 55, 59-73 were rejected under 35 USC §112, 1st paragraph for non-enablement.

Examiner states that the nature of the invention is "the method for treating a disease, condition or disorder modulated by a cannabinoid receptor antagonist..."

This is not entirely correct since most of the claims were directed to compounds and not methods of use. Combining the 112 arguments for compounds with the method claims is contrary to established law as explained below.

Applicants would also like to bring to the Examiner's attention that controlling precedent requires that the USPTO accept the objective truth of Applicants' teachings of enablement unless there is a reason to doubt these teachings. Applicants respectfully submit that there is no reason to doubt the objective truth of the statements contained within the Specification upon which Applicants rely for enabling support of their compounds.

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing the defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for the enabling support. In Re Marzocchi, 439 F.2d 220,222 (CCPA 1971).

The burden is on the Examiner to come forward with *evidence* as to why assertions of utility should not be accepted. In the instant case, the Examiner asserts that the exact role of the cannabinoid receptor is still under investigation and cites Barth, et al. which was published in 1999 (6 years old). Since this publication much has been learned about cannabinoid antagonists as evidenced by the two review articles submitted with the Supplemental Information Disclosure Statement filed on October 25, 2005. See, Smith, et al., "Recent advances in the research and development of CB1 antagonists" IDrugs, **8**(1), 53-56 (2005); Muccioli, G.G., et al, "Current Knowledge on the Antagonists and Inverse Agonists of Cannabinoid Receptors" Current Medicinal Chemistry, **12**, 1361-1394 (2005); and references cited therein, as well as the numerous references cited by Applicants in the earlier submitted Information Disclosure Statements. Clearly, compounds that bind to the cannabinoid-1 receptor have pharmacological utility, in particular, for use in treating obesity and associated metabolic disorders.

Examiner queries which receptor Applicants' compounds modulate. Applicants would like to point out to the Examiner the numerous references within the specification to the CB-1 receptor. Not only do the Applicants point out the

particular receptor, but also the fact that the compounds act as a CB-1 receptor antagonist (or inverse agonist).

> "The present invention provides compounds of Formula (I) or (II) that act as cannabinoid receptor ligands (in particular, CB1 receptor antagonists)" emphasis added. See, page 3, lines 17-18.

> "Compounds of the present invention have been shown to be useful cannabinoid receptor ligands (in particular, CB1 receptor antagonists). emphasis added. See, page 8, lines 3-2.

> "In yet another embodiment of the present invention, a method for treating a disease, condition or disorder modulated by a cannabinoid receptor (preferably, a CB1 receptor) antagonists in animals that includes the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of the present invention (or a pharmaceutical composition thereof)." See, page 8, lines 15-19

> "The present invention further provides a method of treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists in an animal that includes administering to an animal in need of such treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition comprising an effective amount of a compound of the present invention and a pharmaceutically acceptable excipient, diluent, or carrier. The method is particularly useful for treating diseases, conditions and/or disorders modulated by cannabinoid receptor (in particular, CB1 receptor) antagonists.
> emphasis added. See, the page 33, lines 17-24.

More importantly, the pharmacological data section provides evidence that the compounds of the present invention bind to the CB-1 receptor. It does not matter which disorder, condition or disease is being treated to show utility of a compound so long as there exists a disorder, condition or disease that is mediated by binding to that particular receptor. The literature evidences more than sufficient uses for compounds that bind to the cannabinoid receptors (in particular, the CB-1 receptor). As stated by Applicants in the specification, CB-1 binding activities of 4 nM and 2 nM were observed for Examples 1A-2 and 1A-3, respectively. See, page 52, lines 25-26 of the specification.

Although Examiner acknowledged the assays beginning at page 51, she failed to see the significance of such assays. Applicants clearly stated that the binding assays were designed to detect compounds that inhibit the binding of [^{3}H] SR141716A (a known selective radiolabeled CB-1 ligand) and [^{3}H] 5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol; a known radiolabeled CB-1/CB-2 ligand) to their respective receptors. See page 52, line 33 – page 53, line 2. Applicants also provided references which describe the significance of the binding assays.

> "Bioassay systems for determining the CB-1 and CB-2 binding properties and pharmacological activity of cannabinoid receptor ligands are described by Roger G. Pertwee in "Pharmacology of Cannabinoid Receptor Ligands" Current Medicinal Chemistry, 6, 635-664 (1999) and in WO 92/02640 (U.S. Application No. 07/564,075 filed August 8, 1990, incorporated herein by reference)." Page 52, lines 28-32

After each of the headings of the *in vivo* assays, a brief description is provided which outlines the utility of the test. For example, for food intake, "the following screen was used to evaluate the efficacy of test compounds for inhibiting food intake in Sprague-Dawley rats after an overnight fast". This is a standard test for evaluating compounds for use in treating obesity or weight-control.

Examiner states that the absence of evidence of functional treatment (i.e., no correlation to treatment in humans) lacks enablement. She goes on to assert that "Applicants' assertions either that the compounds would be effective or that the compounds are effective are not enough." Courts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an immediate benefit to the public and thus satisfies the utility requirement. *Nelson v. Bowley*, 626 F.2d 853, 206 USPQ 881 (1980). Similarly, courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition.

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may

> establish a practical utility for the compound in question. Successful *in vitro* testing will marshall resources and direct the expenditure of effort in further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility." Cross v. Iizuka, 753 F.2d 1040, 1051, 224 USPQ 739, 739, 747-48 (Fed. Cir. 1985).

Clearly, Examiner's statements are contrary to existing law. Applicants have provided extensive descriptions of biological assays used to evaluate and predict the utility of the compounds of the present invention. In addition, the binding data observed for the compounds exemplified in the Examples 1A-2 and 1A-3 are included on page 52, lines 25-26 which clearly indicate the binding affinity of the compounds to the CB-1 receptor. As pointed out in the specification on page 52, line 33 – page 52, line 2, Applicants compared the compounds of the present invention with SR141716 (a known CB-1 antagonist) to determine binding affinity for the CB-1 receptor. The numerous references submitted through the Information Disclosure Statements provide more than ample evidence that a correlation exists between therapeutic indications and compounds that bind to the CB-1 receptor. SR141716A (also known under the tradename Acomplia™ or the generic name rimonabant) is currently before the FDA for approval for use in treating obesity and related metabolic disorders. Clearly, a nexus exists between compounds that act as CB-1 antagonists and its therapeutic use. Examiner has provided no current evidence to the contrary.

Method Claims 59, 64 and 69 (and dependents thereon) have been amended to the treatment of Obesity which has a clear nexus between the action of a compound as a CB-1 antagonist and the loss of weight for the treatment of Obesity as evidenced by the human clinical trials conducted with the known CB-1 antagonist, rimonabant (SR141716A) and before the FDA for approval for the treatment of Obesity in humans.

II. Claims 65 and 69 were rejected under 35 USC §112, 1st paragraph for non-enablement.

Examiner objects to the use of the term pharmaceutical agent as being indefinite. Since the method claims 65 and 69 have been amended to the treatment of Obesity, the second ingredient has been designated as one or more anti-obesity agents which have been incorporated into the claims from the now cancelled

dependent claims 66-67 and 70-71, respectively. Applicants respectfully submit that these amendments to the claims render the rejection moot.

Although Applicants have limited the method of use claims to the treatment of Obesity to expedite the allowance of the current application, Applicants reserve the right to pursue other indications through continuation application(s).

III. Claims 59-73 were rejected under 35 USC §112, 1st paragraph for non-enablement.

Examiner asserts that the combinations lack enablement. Claims 59 and 64 are not directed to combinations; therefore, Examiner's rejection is illogical with respect to these claims. Claims 60, 65 and 69 (including dependents thereon) have been amended to include only those additional pharmaceutical agents that are useful for the treatment of Obesity which include the anti-obesity agents listed in the now cancelled dependent Claims 61-63, 66-68 and 70-71.

There is more than ample description in the specification for choosing the appropriate anti-obesity agent (page 35, line 12 through page 37, line 6) and the dosage range that could be used (see, page 38, lines 20-32). Examiner makes conclusory remarks that the combination is wholly inoperable without any supporting evidence.

As discussed above, controlling precedent requires that the USPTO accept the objective truth of Applicants' teachings of enablement unless there is a reason to doubt these teachings. Applicants respectfully submit that there is no reason to doubt the objective truth of the statements contained within the Specification upon which Applicants rely for enabling support of their combinations. See, In Re Marzocchi, 439 F.2d 220,222 (CCPA 1971).

IV. Claims 59-73 were rejected under 35 USC §112 1st paragraph as failing to comply with the written description requirement.

Examiner asserts that Claims 59-73 encompass unidentified diseases, disorders and conditions associated with the cannabinoid receptors. Applicants respectfully submit that the amendments to the claims to the treatment of Obesity renders this rejection moot.

As discussed above, a clear nexus exists between the action of compounds as CB-1 antagonists and the treatment of Obesity as evidenced by the human clinical trials and pending NDA for rimonabant (SR141716A). Applicants stated several times through out the specification that the compounds of the present invention are preferably CB-1 antagonists. The binding data observed for the compounds exemplified in the Examples 1A-2 and 1A-3 are included on page 52, lines 25-26 which clearly indicate the binding affinity of the compounds to the CB-1 receptor. As pointed out in the specification on page 52, line 33 – page 52, line 2, Applicants compared the compounds of the present invention with SR141716 (a known CB-1 antagonist) to determine binding affinity for the CB-1 receptor. The numerous references submitted through the Information Disclosure Statements provide more than ample evidence that a correlation exists between therapeutic indications and compounds that bind to the CB-1 receptor. SR141716A (also known under the tradename Acomplia™ or the generic name rimonabant) is currently before the FDA for approval for use in treating obesity and related metabolic disorders in humans. Clearly, a nexus exists between compounds that act as CB-1 antagonists and its therapeutic use. Examiner has provided no current evidence to the contrary.

V. Claims 60, 61, 65, 66, 67, 70 and 71 were rejected under 35 USC §112 2nd paragraph as being indefinite.

Examiner objects to the use of the terms "agent" and "analog." Applicants respectfully submit that the amendment of Claims 60, 65 and 69 render this rejection moot. As discussed above, there is more than ample description of the various anti-obesity agents in the specification on page 35, line 12 through page 37, line 6 that may be used in the practice of the present invention. Several representative examples of anti-obesity agents are specifically listed with references which discuss in detail how to make and use those agents.

Analog is a well established term that those of skill in the art would recognize as meaning a moiety that may differ in structure but has similar function. There is nothing ambiguous about a functionally equivalent moiety and one of skill in the art could easily ascertain whether a moiety is functionally the same or different. Therefore, the term analog is not indefinite.

§101 Rejections

I. Claims 65 and 69 were rejected under 35 USC §101 for lack of utility.

Applicants respectfully submit that the amendments to Claims 65 and 69 render this rejection moot. As discussed above, the compounds of the present invention have been shown to be CB-1 antagonists (or inverse agonists) and therefore have proven utility for treatment of obesity. The additional pharmaceutical agents have been limited to those agents which act as anti-obesity agents. Since the methods of treatment have been limited to treating obesity, it is reasonable to believe that a combination of a CB-1 antagonist with known anti-obesity agents would be useful for treating obesity. Examiner has provided no evidence to the contrary.

Based on the foregoing arguments and the amendments to the claims, Applicants respectfully submit that Claims 1-4, 7-11, 30, 31, 34-36, 42, 43, 49, 55, 59, 60, 64, 65, 69, 72 and 73 are in condition for allowance.

Respectfully Submitted:

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